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(54) Title: TOPICAL NIFEDIPINE PREPARATIONS FOR THE CONSERVATIVE TREATMENT OF FUNCTIONAL PATHOLOGIES OF THE ANAL CANAL

(57) Abstract

Pathologies of the anal canal, acute and chronic fissures, rhagades, spasm, haemorrhoids and tenesmus, as well as ischaemic cholitis, bladder tenesmus and spasm are treated with topical preparations (e.g. suppositories) containing nifedipine (a known calcium antagonist), alone or in combination with antiinflammatory agents, mesclepine or other drug effective in the treatment of ulcerous recto-cholitis or aspecific proctitis or with local anaesthetics such lidocaine or carbocaine.

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Topical Nifedipine preparations for the conservative treatment of functional pathologies of the anal canal.

The present invention relates to the new use of Nifedipine, a well known active principle commonly used against heart and circulatory disorders. The new use is geared towards treatment of functional pathologies of the anal canal.

It is known from the literature that Nifedipine, that is a dimethyl ester of 1,4 dihydro-2,6 dimethyl-4-(2-nitrophenyl)-3,5-pyridinecarboxylic acid, is effective in the treatment of cardiovascular diseases and for that purpose oral administration is recommended.

Pathologies of the anal canal, acute and chronic fissure, haemorroids and tenesmus, are extremely common. About 30-40% of the population suffer from proctologic pathologies at least once in their lives. The disorders that derive from them are generally more annoying than dangerous. Therapy can be either conservative or surgical.

Proctologic diseases are eventually eradicated by a careful employment of surgical techniques, which have undergone a remarkable development in recent times but do indeed represent a defeat for pharmacological therapies.

Non invasive therapies are known but they have so far resorted to anti-inflammatory drugs as disclosed by W.Klug and H.G.Knoch in Colo-Proctology

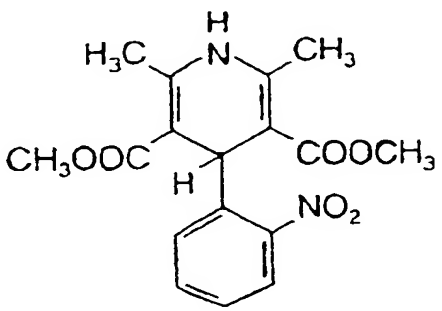
(1993) 1, pp 22-28, and by McDonald et al. in the British Journal of Surgery (1983), 70, pp.25-26 and to other preparations from which Nifedipine was excluded.

Aim of the present invention is to propose the use of Nifedipine in medicaments for the treatment of proctologic pathologies like anal fissure, anal tenesmus and haemorroids, and to outline the main features of a therapy based on the above compound.

Such an aim has been accomplished thanks to the use of Nifedipine by local external application in therapies against pathologies comprising anal rhagades, rectal tenesmus, anal spasm, haemorroids, in suppository form for the treatment against ischemic cholitis, bladder tenesmus and as a gel, cream or ointment by local application or in preparation colonoscopy and cystoscopy.

The present invention also comprises the use of Nifedipine in association with pharmaceuticals such as local anaesthetics like lidocaine, carbocaine, non-steroidal or caustic antiinflammatories, mesclepine, and with any pharmaceutical against ulcerous recto-cholitis and aspecific proctites.

Nifedipine is a dihydropyridine whose structure is shown in Figure 1 below:



Part of its strong activity towards biological systems can be accounted for by the presence of the heterocyclic Nitrogen atom and the nitrated benzene ring which has enhanced electrophilic properties. Moreover, the double carboxy functionality confers a remarkable polarity to the handles and shifts the pyridine ring electrons in such a way as to drastically augment its reactivity in terms of a decrease in its inherent nucleophilicity given by the Nitrogen lone pair of electrons that becomes less available as such.

Its interaction with biological systems is by and large determined by the fact that as a dihydropyridine, it is a calcium antagonist at present administered only orally for the treatment of cardiovascular disorders on the basis of the fact that it induces relaxation of the vascular walls.

The same mechanism can well be advocated for the effectiveness of Nifedipine against pathologies of the anal canal like anal fissure, anal tenesmus and haemorroids.

In the present specification its efficacy when used as a gel for treatment of disorders like acute anal fissure, anal tenesmus,and first and second degree haemorroids is shown. All of the above diseases can be accounted for by a marked hypertonicity of the sphincter.

Targeting and overcoming sphincter hypertonicity leads to efficaceous functional

treatments of several proctologic pathologies and disorders due to organic pathologies like rectal tenesmus during ulcerative cholitis of the rectum.

Sphincter hypertonicity is often associated with other contributory causes like mechanical lesions given by hard stools, and skin lacerations in acute enteritis, ulceration in intra-anal thrombosis, cryptitis and overuse of laxatives.

Sphincter hypertonicity of the continual type, in its internal region, is brought about by an inflammatory infiltrate from an anal skin lesion, whilst, concomitantly, the external sphincter responds with cramp-like contractions.

This sort of cause-to-effect phenomenology becomes a vicious circle whose severity is proven by its very low tendency to remission.

In the above scenario, Nifedipine has been proven to play a crucial role in inhibiting the flow of Ca++ ions into the sarcoplasm of the smooth muscle cells which is known to cause a contraction of the muscle fibres.

Hence its local use as a gel yields to a relaxation of the internal anal region of the sphincter.

Ancillarily, Nifedipine has been advantageously proven by experimental studies to have an antiinflammatory action, a modulating effect on the microcirculation and an ability to act locally.

This further action quenches the inflammation

which is known to confer momentum to the pathologic interactions that establish between the internal and the external regions of the sphincter and can be advocated in the proctologic pathologies which are sustained by a hyertonicity of the internal and external anal sphincter.

Use of Nifedipine in association with pharmaceuticals such as local anaesthetics, lidocaine, carbocaine and alikes is also viable. Furthermore its association with non-steroidal or caustic antiinflammatories, mesclepine and with whichever pharmaceutical with therapeutical viability within therapies against ulcerous recto-cholitis and aspecific proctites has been seen to yield to positive results.

These and other features will be more readily apparent from the following examples offered to illustrate but not limit the invention.

Clinical trials were conducted on 423 patients suffering from anal fissure, anal tenesmus and haemorroids. These were subdivided into six groups, of which three control groups underwent standard treatments according to traditional conservative protocols, while the other three groups of patients were treated by local application of Nifedipine gel.

The patients were subdivided into 3 groups:

Group 1: 283 individuals suffering from acute anal fissure.

Group 2: 60 individuals suffering from haemorroids.

Group 3: 80 individuals suffering from anal tenesmus,

48 of whom had an associated ulcerative cholitis of the rectum.

A selection was made and patients were not admitted to the groups in case of presumed or confirmed pregnancy, chronic anal fissure warranting surgery, third or fourth degree haemorroids, allergy to nifedipine.

All groups were similar in terms of age and sex, and they were further subdivided into two subgroups: the control patients who received a standard conservative therapy that consisted of a suitable diet, the use of laxatives and the local application of a gel containing a local anaesthetic and/or anti-inflammatory drugs, in association with an anal dilator; and the Nifedipine patients whose ptotocol consisted of the local application of 5 mg Nifedipine gel aliquots every 12 hours for a 21 day long period.

Every single patient underwent a standard clinical examination, proctoscopy and anorectal manometry with pressure readings in relaxation and contraction. Furthermore they were asked to answer a questionnaire wherein they could appraise the pain and symptoms they suffered from by categorising them as persistent, modest, or absent.

The above tests were conducted right before the beginning of treatment as well as on its 14th and 21st days.

Example 1. Patients suffering from anal fissure.

Two subgroups with 141 and 142 patients suffering from the above and aged 47 ± 10 years respectively were considered.

Clinical and manometer examinations showed that 80% of the patients were affected by substantial hypertonicity. A total remission from acute anal fissure was recorded in 95% of the patients treated with Nifedipine, whereas the same positive results were observed in only 50% of the control patients; pain was seen to be absent, modest and persistent respectively in 65%, 30% and 5% of the patients in the Nifedipine group, whereas patients in the control group were as many as 40%, 30% and 30%. Moreover, anorectal manometry showed normalisation of the sphincter tone in as many as 80% of the patients in the Nifedipine subgroup, against the mere 35% of the control patients.

The results are summarised in table 1 below.

Table 1

Group	No. of patients	Clinical evaluation of pain (%)			Anorectal Manometry normalization of sphincter tone (%)	Total remission (%)
		absent	modest	persistent		
Nifedipine Subgroup	141	65	30	5	80	95
Control subgroup	142	40	30	30	35	50

Example 2. Patients suffering from haemorroids.

Two subgroups made up of 31 and 29 patients aged 45 ±10.8 years were monitored. Only patients affected by sphincter hypertonicity were considered, and this was detected by manometer examination. After just 14 days of treatment, patients affected by haemorroids that showed a substantial improvement symptomwise and a reduction in the degree were as many as 67% in the Nifedipine group, whereas they reached a mere 27% in the control group. The above percentages sored to 70% and 38% respectively, at the end of the 21 days of treatment. Moreover, anorectal manometry showed a more drastic reduction in hypertonicity in the patients of the Nifedipine group, in comparison with those of the control group, but statistical analysis revealed the difference not to be significant.

The results are shown in table 2 below.

Table 2

Group	No. of patients	Anorectal Manometry: normalization of sphincter tone (%)	Clinical improvement of the symptoms (%)
Nifedipine subgroup	31	61	70
Control subgroup	29	38	38

Example 3. Patients suffering from anal tenesmus.

Two groups made up of 38 and 42 patients aged 38 ±9.8 years were considered. In as many as 93% of the patients of the Nifedipine group, symptoms disappeared after only a few days, compared with 52% in the control group. Patients suffering from anal tenesmus associated with ulcerative cholitis of the rectum were present in equal amounts in both groups, and for these, remission showed to be slower.

The results are summarised in Table 3 below.

Table 3

Group	No. of patients (*)	Anorectal Manometry: Normalization of sphincter tone(%)		Remission of the symptoms (%)	
		14 days	21 days	14 days	21 days
Nifedipine subgroup	38 (23*)	80 (74*)	93 (82*)	93 (82*)	100 (95*)
Control subgroup	42 (25*)	52 (36*)	64 (48*)	52 (44*)	65 (56*)

Considering the positive results of the present clinical experience, it can be seen that the therapeutic use of Nifedipine, which at present concerns cardiovascular pathologies, should be extended with local use, to pathologies like anal fissure, anal tenesmus, and haemorroids associated with sphincter hypertonicity. On the basis of other experimental studies conducted by Yousif and Triggle, and published in the Can. J. Physiol Pharmacol 1985, 63, pp.193-195,

the applicant suggests that other pathologies such as ischemic cholitis, bladder tenesmus and bladder spasm as well as preparation for endoscopic examinations like colonoscopy and cystoscopy could benefit from Nifedipine administered in the form of suppositories or a gel.

CLAIMS.

1. The use of Nifedipine in making a medicament, which medicament is for local external application in therapies against pathologies comprising anal rhagades, rectal tenesmus, anal spasm, haemorroids.

2. The use of Nifedipine in making a medicament, according to claim 1, wherein the medicament is in the form of a gel, cream or ointment, also useful in preparation for colonoscopy and cystoscopy.

3. The use of Nifedipine in making a medicament, which medicament is for treatment against ischemic cholitis, bladder tenesmus and spasm, in suppository form.

4. The use of Nifedipine according to any of the preceding claims in association with pharmaceuticals such as local anaesthetics like lidocaine, carbocaine; non-steroidal or caustic antiinflammatories; mesclepine, and with any pharmaceutical against ulcerous recto-cholitis and aspecific proctites.

5. Topical preparation for therapies targeting anal rhagades, rectal tenesmus, anal spasm, haemorroids, characterised by the fact that it comprises Nifedipine ranging between 0.5% and 30% by weight, lidocaine

hydrochloride ranging between 0.25 and 15% by weight, and carriers and eccipients *quantum sufficit*.

6. Topical preparation according to claim 5, wherein the carriers and eccipients comprise polyethyleneglycol, carboxymethylcellulose, glycerine, methyl-p-hydroxybenzoate, ethyl-p-hydroxybenzoate, propyl-p-hydroxybenzoate, sodium benzoate and water.